TUMOR ANTIGEN PRESENTATION INDUCER CONSTRUCTS AND USES THEREOF

BACKGROUND

[0001] Although neoplastic transformation invariably involves tumor-associated antigen (TAA) emergence, self-tolerance mechanisms often limit TAA-specific T lymphocyte activation. Accordingly, though immune checkpoint blockade (e.g. anti-CTLA-4 and anti-PD-1/PD-L1) has revolutionized cancer immunotherapy, a large patient percentage remains non-responsive due to lack of pre-existing TAA-specific T cells (Yuan et al., 2011 *PNAS* 108:16723-16728). Treatments that increase endogenous TAA-directed T cell responses may be required for long-lasting, broad-acting anti-tumor immunity.

[0002] Numerous tumor vaccine approaches have attempted to overcome TAA tolerance, but have exhibited limited efficacy due to heterogeneity in expression of TAAs. For example, transformed cells that lack or downregulate TAA expression can persist post-vaccination and promote relapse. Because neoplastic cell TAA landscapes are heterogeneous and dynamic, vaccine approaches that rely on pre-defined TAA mixtures have been minimally efficacious, and therapies that overcome immunologic tolerance to multiple, diverse TAAs, and adapt with evolving TAA expression patterns are needed.

SUMMARY

[0003] Described herein are tumor-associated antigen (TAA) presentation inducer constructs and uses thereof. One aspect of the present disclosure relates to tumor-associated antigen (TAA) presentation inducer constructs comprising: a) at least one innate stimulatory receptor (ISR)-binding construct that binds to an ISR expressed on an antigen-presenting cell (APC), and b) at least one TAA-binding construct that binds directly to a first TAA that is physically associated with tumor cell-derived material (TCDM) comprising one or more other TAAs, wherein said ISR-binding construct and said TAA-binding construct are linked to each other, and wherein the TAA presentation inducer construct induces a polyclonal T cell response to the one or more other TAAs.

[0004] Another aspect of the present disclosure relates to a pharmaceutical composition comprising the TAA presentation inducer construct described herein.

[0005] Another aspect of the present disclosure relates to one or more nucleic acids encoding the TAA presentation inducer construct described herein.

[0006] Another aspect of the present disclosure relates to one or more vectors comprising one or more nucleic acids encoding the TAA presentation inducer construct described herein.

[0007] Another aspect of the present disclosure relates to a host cell comprising one or more nucleic acids encoding the TAA presentation inducer construct described herein, or comprising one or more vectors comprising one or more nucleic acids encoding the TAA presentation inducer construct described herein.

[0008] Another aspect of the present disclosure relates to a method of making the tumor-associated antigen (TAA) presentation inducer construct described herein comprising: expressing one or more nucleic acids encoding the TAA presentation inducer construct described herein, or one or more vectors comprising one or more nucleic acids encoding the TAA presentation inducer construct described herein, in a cell.

[0009] Another aspect of the present disclosure relates to a method of treating cancer comprising administering the tumor-associated antigen (TAA) presentation inducer construct described herein to a subject in need thereof.

[0010] Another aspect of the present disclosure relates to a method of inducing major histocompatibility complex (MHC) presentation of peptides from two or more tumor-associated antigens (TAAs) by a single innate stimulatory receptor-expressing cell simultaneously in a subject, comprising administering to the subject the TAA presentation inducer construct described herein.

[0011] Another aspect of the present disclosure relates to a method of inducing innate stimulatory receptor-expressing cell activation in a subject, comprising administering to the subject, the tumor-associated antigen (TAA) presentation inducer construct described herein.

[0012] Another aspect of the present disclosure relates to a method of inducing a polyclonal T cell response in a subject, comprising administering to the subject the tumor-associated antigen (TAA) presentation inducer construct described herein.

[0013] Another aspect of the present disclosure relates to a method of expanding, activating, or differentiating T cells specific for two or more tumor-associated antigens (TAAs) simultaneously, comprising: obtaining T cells and innate stimulatory receptor (ISR)-expressing cells from a subject; and culturing the T cells and the ISR-expressing cells with the TAA presentation inducer construct described herein in the presence of tumor cell-derived material (TCDM), to produce expanded, activated or differentiated T cells.

[0014] Another aspect of the present disclosure relates to a method of treating cancer in a subject, comprising administering to the subject the expanded, activated or differentiated T cells prepared according to the method described herein.

[0015] Another aspect of the present disclosure relates to a method of identifying tumor-associated antigens in tumor cell-derived material (TCDM) comprising: isolating T cells and enriched innate stimulatory receptor (ISR)-expressing cells from a subject; culturing the ISR-expressing cells and the T cells with the TAA presentation inducer construct described herein in the presence of tumor cell-derived material (TCDM), to produce TAA presentation inducer construct-activated ISR-expressing cells, and determining the sequence of TAA peptides eluted from MHC complexes of the TAA presentation inducer construct-activated ISR-expressing cells; and identifying the TAAs corresponding to the TAA peptides.

[0016] Another aspect of the present disclosure relates to a method of identifying T cell receptor (TCR) target polypeptides, comprising: isolating T cells and enriched innate stimulatory receptor (ISR)-expressing cells from a subject; culturing the ISR-expressing cells and the T cells with the TAA presentation inducer construct described herein in the presence of tumor cell-derived material (TCDM), to produce TAA presentation inducer construct-activated ISR-expressing cells and activated T cells, and screening the activated T cells against a library of candidate TAAs to identify the TCR target polypeptides.